Remarks

Claims 1-62, 68-75 and 82-87 are pending. Claims 48, 56, 60, 62, 68, 70, and 74 were amended to more clearly claim what Applicants perceive to be their invention. Claims 82-86 were cancelled.

Claims 48, 69, 70, 74, and 75 were amended to recite "wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid". These amendments find support at least on page 36, lines 19-25, and, in particular, on lines 21-25, where capture tags are described as including nucleic acid molecules and proteins ("As used herein, a capture tag is any compound that can be attached either covalently or non-covalently with a molecule of choice including a nucleic acid molecule or a protein molecule, and which can be used to at least separate, identify, associate, denote, or mark compounds or complexes having the capture tag from those that do not."). Applicants note that it is proper to exclude from the claimed invention some features specifically disclosed as part of the invention. See *In re Johnson*, 558 F.2d 1008, 194 USPQ 187 (CCPA 1977) (stating that the "specification, having described the whole, necessarily described the part remaining"). Support for the amendment to Claim 48 can also be found at least in previously presented claims 83-85.

Claim 53 was amended to recite that the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. This finds support at least on page 36, lines 26-30.

Claims 56, 71, and 87 were amended to recite "wherein the capture tag is not a nucleic acid". This amendment finds support at least on page 36, lines 19-25, and, in particular, on lines 21-25, where capture tags are described as including nucleic acid molecules and proteins.

Claim 60 was amended to recite "the method of claim 59" rather than "the method of 59".

Claim 62 was amended to recite "wherein the 3' end of the rolling circle replication primer portion is extended to replicate the amplification target circles". This amendment finds support at least in original claim 63.

Claim 68 was amended to recite "and wherein the capture tag is not a nucleic acid,". This amendment finds support at least on page 36, lines 19-25, and, in particular, on lines 21-25, where capture tags are described as including nucleic acid molecules and proteins.

Claim 72 was amended to correct a typographical error.

Summary of Interview

Applicant would like to thank Examiner Calamita and her Supervisor for their comments during phone call of March 20, 2007 to discuss the Office Action mailed December 13, 2006.

Regarding the substance of the Office Action, the rejections under 35 U.S.C. § 103 was discussed. Specifically, the combination of the method of Lizardi '229 with the antibody-oligonucleotide of Schweitzer et al. was discussed. The Examiner's Supervisor supported the Examiner's arguments based on the fact that a capture tag could be a nucleic acid and that nucleic acids can be altered easily to achieve the specific oligonucleotides previously presented in the claims. Applicants suggested amending certain claims to exclude where the capture tags could be nucleic acids. Applicants were invited to present such amendments in the current Amendment and Response.

In addition, Applicants described the method of Lizardi '229, by directing the Examiner and her Supervisor to BP-RCA and the fact that BP-RCA requires a nucleotide to nucleotide interaction. Applicants directed the Examiner and her Supervisor's attention to the requirement of a ligation step that, if an antibody was introduced or substituted for the probe or probe/primer of Lizardi '229, the fundamental principle of operation would be altered. The Examiner's Supervisor invited the Applicant to submit such an argument, which Applicants have included below.

Rejections Under 35 U.S.C. § 103

1. Claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229; Lizardi '229) in view of Schweitzer et al. (PNAS 2000). Applicants respectfully traverse this rejection.

(i) The Law

In order for a reference or a combination of references to make obvious a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

(ii) The Cited Art

Lizardi '229 discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. In the form of the method relied on in the rejection, referred to as bipartite primer rolling circle amplification (BP-RCA), RCA of the ATC depends on the formation of a primer by target-mediated ligation (see Lizardi '229, column 41, lines 5-20). As such, a critical feature of BP-RCA requires that a probe and a combination probe/primer oligonucleotide hybridize to adjacent sites on a target sequence in the presence of a nucleic acid molecule having the target sequence, thus allowing the probes to be ligated together (Id.). The ligated primer can then be used to prime replication of its cognate ATC (Id.). As acknowledged in the Office Action on page 6, lines 20-21, Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the capture tag is not a nucleic acid.

Schweitzer et al. discloses a method of detecting protein antigens referred to as "immunoRCA". In immunoRCA, an oligonucleotide primer is covalently attached to an antibody at its 5' end. In the presence of circular DNA, DNA polymerase, and nucleotides, the oligonucleotide primes amplification of the circular DNA. Schweitzer et al. also fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid.

(iii) Summary of Why the Rejection Cannot Be Maintained

Independent claims 1, 48, 53, 56, 68-71, 73-75 and 87 all require, inter alia, that:

(a) the cDNA strands associate with the rolling circle replication primers,

(b) this association occur via the capture tag, and

(c) the capture tag is not a nucleic acid.

The cited publications, either alone or in combination, fail to disclose, suggest or motivate an alteration of the method of Lizardi '229 to associate the probe-primers of Lizardi '229 with the target nucleic acid of Lizardi '229 using the antibody-primer conjugate of Schweitzer et al.

The crux of the present rejection is based on the following logic:

(a) Lizardi '229 discloses association of a rolling circle replication primer with a target nucleic acid via nucleic acid base pairing,

(b) Schweitzer et al. discloses an antibody-rolling circle replication primer conjugate and the association of the rolling circle replication primer with a protein via the antibody portion of the antibody-rolling circle replication primer conjugate, and

(c) those of skill in the art allegedly would be motivated to alter the method of Lizardi '229 to use a non-nucleic acid moiety (such as an antibody) to associate the rolling circle replication primer with the target nucleic acid in the method of Lizardi '229.

Applicants submit that this rejection fails for at least the following three reasons:

(a) there is no disclosure, suggestion, or motivation to make the alleged alteration in the cited publications, the Office Action provides no evidence that supports the conclusion of the rejection that those of skill in the art would be motivated to make the alleged alteration, the alleged (and completely unsupported) motivation recited in the Office Action would not, in fact, motivate the required alteration,

(b) the rejection is clearly based on impermissible hindsight as evidenced by the implicit logic of the rejection, and

(c) the alleged alteration cannot support the alleged obviousness of the claimed method because the alleged alteration would impermissibly alter a fundamental principle of operation of the method of Lizardi '229.

Any one of these reasons alone is fatal to the present rejection.

(iv) The Rejection Fails to Provide or Support Any Sufficient Motivation to Alter the Prior Art as Required

The passages cited in the Office Action fail to disclose or suggest the claimed use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is not a nucleic acid. Further, no relevant motivation to combine the references is provided in the Office Action. The motivation offered in the Office Action is not relevant to the claimed method.

The method of claims 1, 48, 53, 56, 68-71, 73-75 and 87 involve synthesis of cDNA from a nucleic acid sample using an RT primer. As part of the method, the cDNA is associated with a rolling circle replication primer. Significantly, the claims require that the association between the rolling circle replication primers and cDNA occurs via the capture tag (see, for example, step (c) of claim 1). Further, the claims require that the capture tag is not a nucleic acid. Claims 1, 48, 53, 56, 68-71, 73-75 and 87 variously differ on the component used in the method that comprises the capture tag (for example, the rolling circle replication primer, the cDNA or the RT primer).

The rejection fails to point out where the cited publications disclose or suggest each and every limitation of the claims. The Office Action alleges (page 2, lines 20-23) that Lizardi '229 teaches "mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling circle replication primers" [sic]. The Office Action admits on page 6, lines 16-17, that Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid." The Office Action fails to allege that Schweitzer et al. discloses or suggests use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, in the first instance, the Office Action fails to allege that the cited publications disclose or suggest all of the claimed limitations. In particular, the Office Action fails to provide any evidence that either Schweitzer et al. or Lizardi '229 disclose or suggest association of a rolling circle replication primer and cDNA that occurs via a capture tag.

The Office Action alleges on page 7, lines 10-13, that one of skill in the art would have been motivated to use the method of attaching an antibody capture tag to a primer, as allegedly taught by Schweitzer with the method of amplifying target nucleic acids as taught by Lizardi '229 in order to have a "versatile ultrasensitive method of antigen detection". Further, in the telephone interview with the Examiner, the Examiner clarified that Schweitzer et al. was merely being used for the general teaching of an oligonucleotide (primer) attached to an antibody (capture tag) and alleged that an ordinary practitioner would have been motivated to use the

method of attaching an antibody capture tag to a primer, as taught by Schweitzer et al., with the method of amplifying target nucleic acids as taught by Lizardi '229 in order to expand the genus of analytes which can be detected using RCA. Applicants note, however, that the claims are not drawn to an "expanded genus of analytes" and there is no benefit to be gained from a "versatile ultrasensitive method of antigen detection". The claims are drawn to methods of amplifying and using messenger RNA, a very specific and narrow class of "analytes". The motivation to expand the genus of analytes which can be detected using RCA is not relevant to the claimed subject matter. Thus, the sole motivation to combine the references provided in the Office Action is ineffective to make the combination obvious. Furthermore, the Office Action fails to provide any evidence to support the allegation that one of skill in the art would be motivated to combine the references to reach the currently claimed subject matter. Nothing in the cited publication provides evidence even for the insufficient motivation presented in the rejection. This does not satisfy the Examiner's burden of providing evidence of a teaching, motivation or suggestion present in either Lizardi '229 or the Schweitzer et al. reference to combine the oligonucleotide primer-antibody of Schweitzer et al. with the method of Lizardi '229 to achieve the currently claimed subject matter.

As it stands, there is no rationale for combination of the disparate elements of Lizardi '229 and Schweitzer et al. provided and none is apparent. Applicants note in particular that it has not been established, nor is it apparent, how or why one of skill in the art would think that the oligonucleotide/antibody molecule of Schweitzer et al. could or should be used in the BP-RCA method of Lizardi '229. Nowhere in Lizardi '229 is the use of any other molecules, other than the specific probe and a combination probe/primer moieties described. It is the specific relationship and orientation of the probe and the combination probe/primer oligonucleotides with the target sequence (i.e. cDNA) that is taught and required for the method of BP-RCA as described by Lizardi '229 to function. There is no disclosure anywhere in Lizardi '229 or Schweitzer et al. that addresses altering the two oligonulceotide moieties required to for the bipartite primer necessary for priming replication in the BP-RCA method relied upon by the Office Action. The specific nucleotide to nucleotide interaction between the target nucleotide and the rolling circle replication primer portion of the probe/primer is all that is disclosed in Lizardi '229, and Schweitzer et al. provides nothing that would suggest otherwise. Because this

nucleotide to nucleotide interaction is required for the BP-RCA method to function, Applicants submit that one of skill in the art would not be motivated to alter the reaction by removing the probe/primer oligonucleotide from the method of Lizardi '229 and replace the probe/primer with an antibody linked to a primer sequence.

As such, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose each of the elements of claims 1-15, 18-29, and 82 and fail to suggest or provide any sufficient motivation to alter the method of Lizrdi '229 to arrive at the claimed method. Accordingly, for at least these reasons, Lizardi '299 and Schweitzer et al. fail to make claims 1-15, 18-29, 53-58, 61, 68, 70, 71, 73 and 82-87 obvious. For all of the above reasons, Applicants respectfully request withdrawal of this rejection.

(v) The Rejection Relies On Impermissible Hindsight

Applicants submit that the basic premise of the present rejection is based on impermissible hindsight. The core logic of the present rejection is that the specific idea of an antibody with an attached oligonucleotide of Schweitzer et al., can be generalized, modified and applied to the methods of Lizardi '229. However, there is no basis and no support for the adaptation of the particular antibody/primer structure of Schweitzer et al. to the method of Lizardi '229. It seems clear that the rejection has been impermissibly influenced by the present specification. Specifically, Applicants provide, in the present specification, a broad definition of capture tag that equates antibody, antigen, hapten and ligand capture tags with nucleic acid capture tags. Although such a relationship is at the core of the present rejection, it is not described or suggested by the cited publications. The antibody-antigen interaction of Schweitzer et al. is not like or similar to the nucleotide-nucleotide (hybridization) interaction required in Lizardi '229. Thus, it is clear that the rejection impermissibly relies on Applicants' own disclosure to provide the suggestion for the present rejection.

It is not enough to combine cited references with unspecified knowledge in the art without some objective reason to do so. Rather, to make this combination without evidence of such knowledge or the suggestion, teaching or motivation to combine is an impermissible hindsight reconstruction and simply takes the inventor's disclosure as a blueprint for piecing together the prior art in an effort to defeat patentability. (See In re Dembiczak, 50 U.S.P.Q.2d 1614 (Fed. Cir.1999)). Simply put, the motivation to combine references can not come from the

invention itself. (See In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1446 (Fed. Cir.1992).

As discussed above, the Office Action has admitted that Lizardi '229 et al. fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid. The Office Action attempts to explain away such a lack of teaching by alleging on page 7, lines 10-21 that one of skill in the art would have been motivated to include the antibody capture tag attached to an oligonucleotide disclosed by Schweitzer et al. in the methods of Lizardi '229. The Office Action provides that one of skill in the art would have been motivated to use the method of attaching an antibody capture tag to a primer, as allegedly taught by Schweitzer et al. with the method of amplifying target nucleic acids as taught by Lizardi '229 in order to have a "versatile ultrasensitive method of antigen detection". However, this alleged motivation does not lead from the prior art to what is claimed. It is like saying that a desire to be healthy motivates the design of a specific drug. More is required to establish obviousness. This allegation is made relying on the fact that each of the individual pieces allegedly were present at the time of the invention, with no citation to anywhere in any of the cited references to support that their combination was suggested or motivated (see argument above). The Office Action fails to provide any evidence of where in Lizardi '229 or Schweitzer et al. such a motivation, teaching, or suggestion to combine comes from. The present application is the only blueprint for such a combination, and as described above the motivation to combine references can not come from the invention itself. (See In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992).

Thus, the Examiner has not met her burden of establishing that Lizardi '229 or Schweitzer et al. either alone or in combination, disclose or suggest each and every element of claims 1-15, 18-29, and 82. Accordingly, Lizardi '229 or Schweitzer et al., either alone or in combination, do not make obvious claims 1-15, 18-29, 53-58, 61, 68, 70, 71, 73 and 82-87. Applicants respectfully request withdrawal of this rejection.

(vi) The Rejection Requires Alteration of a Fundamental Principle of Operation of the Prior Art

Applicants submit that modification of the method of Lizardi '229 cited in the rejection as suggested in the rejection would change the fundamental principle of operation of the method. In particular, the method of Lizardi '229 requires a nucleotide to nucleotide base pair interaction of the primer and the target sequence to form the bipartite primers required in the BP-RCA method described by Lizardi '229. Eliminating this nucleotide to nucleotide base pair interaction would alter a necessary, and thus fundamental, acpect of the method of Lizardi '229. Thus, for at least these reasons the present rejection cannot be sustained.

A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Lizardi '299 cited in the rejection as suggested in the rejection would alter the fundamental principle of operation of the method and thus for at least this additional reason the present rejection cannot be sustained.

As described above, Lizardi '229 discloses a method of carrying out BP-RCA where RCA of the ATC depends on the formation of a primer by target mediated ligation (see column 41, lines 5-8). The method disclosed by Lizardi '229 requires formation of a rolling circle replication primer by target-mediated ligation of two oligonucleotides: a half probe and a probe/primer. The half probe and a portion of the probe/primer hybridize to a target DNA molecule via base pairing. Thus, association of the primer and the target DNA molecule in Lizardi '229 occurs by a nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and of the half probe and probe/primer, not by interaction of, for example, a hapten or ligand. Efficient and specific ligation of two nucleic acid strands generally requires that the nucleic acid strands be base paired to another strand such that their respective 3' and 5' ends are adjacent to each other. In other words, for the method of BP-RCA to function properly, target-mediated ligation of a probe and a combination probe-primer oligonucleotide must occur; and this requires that the probe and probe-primer hybridize to adjacent sites on the target sequence (see Lizardi '229, column 4, lines 4-11).

In fact, if the nucleotide to nucleotide interaction between the primer and the target DNA molecule does not occur, ligation would not occur and the ATC used in the BP-RCA method will not attach to the primer. Only those ATCs complementary to ligated primers will be amplified (see column 4, lines 29-30, of Lizardi '229). Even if, for the sake of argument, an antibody could be used to bind the probe-primer of Lizardi '229 to the target DNA of Lizardi '229, this would prevent the ligation of the probe and the probe-primer, thus defeating the purpose, and be contrary to the fundamental principles, of Lizardi '229 in having the formation of a rolling circle replication primer be dependent on target-mediated nucleic acid base pairing and ligation of two oligonucleotides. Lizardi '299 states that:

> "In one form of the method, referred to as bipartite primer rolling circle amplification (BP-RCA), RCA of the amplification target circle (ATC) depends on the formation of a primer by target-mediated ligation. In the presence of a nucleic acid molecule having the target sequence, a probe and a combination probe/primer oligonucleotide can hybridize to adjacent sites on the target sequence allowing the probes to be ligated together. By attaching the first probe to a substrate such as a bead or glass slide, unligated probe/primer can be removed after ligation. The only primers remaining will be primers ligated, via the probe portion of the probe/primer, to the first probe. The ligated primer can then be used to prime replication of its cognate ATC. In this way, an ATC will only be replicated if the target sequence (to which its cognate probe/primer is complementary) is present.

Column 4, lines 4-18 (emphasis added).

Use of an antibody such as the antibody taught by Schweitzer et al. to associate the probe or probe/primer to the target DNA of Lizardi '229, as it has been suggested by the Office Action, would prevent ligation and hybridization-based sequence discrimination of the formation of primers in the method of Lizardi '229. Such a change as required by the logic of the present rejection would render the method of Lizardi '229 inoperable. Clearly, such a modification would alter the fundamental principle of operation of the method of Lizardi '229. Such a change in the principle of operation of the method of Lizardi '299, which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, for at least these additional reasons, Lizardi '229 and Schweitzer et al. fail to make claims 1-15, 18-29, 53-58, 61, 68, 70, 71, 73 and 82-87 obvious. For all of the above reasons, Applicants respectfully request withdrawal of this rejection.

(vii) Arguments for Claims 62 and 72

The method of claims 62 and 72 requires the use of RT primers that comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. That is, the claims require use of an RT primer that comprises a rolling circle replication primer portion that is the basis for the association of the rolling circle replication primers with amplification target circles. The claims also require that the rolling circle replication primer portion not be linked to the reverse transcription primer portion via their 5' ends.

The cited passage of Lizardi '229 and Schweitzer et al. fail to disclose or suggest RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. The combination of a rolling circle replication primer and a reverse transcription primer is not even hinted at in the cited publications. In the method of Lizardi '229, the rolling circle replication primer is clearly distinct from and not a part of the target sequence (which is alleged in the rejection to encompass cDNA). Rather, the rolling circle replication primer in the method of Lizardi '229 is part of the combination probe primer that hybridizes to the target sequence and is ligated to the immobilized probe. The method of Lizardi '229 would not be operable if the rolling circle replication primer were part of the target sequence (which would be the result if the rolling circle replication primer were part of a reverse transcription primer used to make cDNA to be used as a target sequence). Nothing in Schweitzer et al. suggests otherwise. The cited publications simply do not disclose or suggest placement of a rolling circle replication primer as claimed and the rejection makes no mention of any motivation to make such a combination reverse transcription primer and rolling circle replication primer. Further, the combination od a reverse transcription primer and a rolling circle replication primer as claimed would render the method of Lizardi '229 inoperable, and thus would impermissibly alter a fundamental principle of operation of the method of Lizardi '229. For all of these reasons, the Office Action fails to establish any basis for obviousness of claims 62 and 72.

In the interview, the Examiner suggested that any reverse transcription primer could be said to include a rolling circle replication primer because the sequence of rolling circle

replication primers can be arbitrarily chosen (to be complementary to the freely chosen sequence of an amplification target circle) and any sequence in a reverse transcription primer could arbitrarily be denominated a "rolling circle replication primer portion." This logic is flawed in a number of respects. First, the claims require that bot the reverse transcription portion and the rolling circle replication primer portion of the RT primer have their own 5' end and require that the reverse transcription primer portion and the rolling circle replication primer portion not be linked via their 5' ends. Two free 5' ends is not a known or standard structure for reverse transcription primers and so the claims require more than a standard reverse transcription primer in which a sequence could be arbitrarily denominated as a rolling circle replication primer portion. Second, to function, both the reverse transcription primer portion and the rolling circle replication primer protion of the RT primer must have their own free 3' end. Otherwise they would not each be capable of priming reverse transcription and rolling circle replication, respectively. Further, the free 3' end of the rolling circle replication primer portion must survive cDNA synthesis primed by the reverse transcription primer portion because the rolling circle replication primer primes rolling circle replication following cDNA synthesis. Two free 3' ends is not a known or standard structure for reverse transcription primers and so the claims require more than a standard reverse transcription primer in which a sequence could be arbitrarily denominated as a rolling circle replication primer portion. For at least these additional reasons, the current rejection cannot be sustained.

It should be noted that during the telephone interview, the Examiner alleged that there was no nexus between the claimed RT primers and the replication of amplification target circles. In response, Applicants have amended claim 62 to include such a nexus. Specifically, Applicants have added the language wherein the 3' end of the rolling circle replication primer portion is extended to amplify the amplification target circles. Thus, the claimed RT primers are not "just primers" in that they are more than a simple nucleotide sequence as they are the basis of two specific reactions requiring two separate targets (reverse transcribing mRNA to cDNA and amplifying amplification target circles).

Therefore, for at least this reason, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 62 and 72.

Accordingly, and for all of the above reasons, Lizardi '229 and Schweitzer et al. fail to make obvious claims 62 and 72. Applicants respectfully request withdrawal of this rejection.

Claims 83-85 have been cancelled. As such, Applicants respectfully submit the current rejection is moot in view of the cancellation of these claims.

2. Claims 16 and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Lizardi (US 2003/0032024 A1; Lizardi '024) Applicants respectfully traverse this rejection.

Applicants note that claims 16 and 17 depend from claim 1 and thus include all of the limitations of claim 1. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claim 1 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, (a) there is no disclosure, suggestion, or motivation to make the alleged alteration in the cited publications, the Office Action provides no evidence that supports the conclusion of the rejection that those of skill in the art would be motivated to make the alleged alteration, the alleged (and completely unsupported) motivation recited in the Office Action would not, in fact, motivate the required alteration; (b) the rejection is clearly based on impermissible hindsight as evidenced by the implicit logic of the rejection; and (c) the alleged alteration cannot support the alleged obviousness of the claimed method because the alleged alteration would impermissibly alter a fundamental principle of operation of the method of Lizardi '229.

Lizardi '024 was not offered to disclose or suggest any of the elements missing from Lizardi '229 and Schweitzer et al. and Lizardi '024 does not disclose or suggest any of the elements missing from Lizardi '229 and Schweitzer et al.

For at least these reasons, Lizardi '229, Schweitzer et al., and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 16 and 17. Accordingly, and for all of the above reasons, Lizardi '229, Schweitzer et al., and Lizardi '024 fail to make obvious claims 16 and 17. Applicants respectfully request withdrawal of this rejection.

3. Claim 30 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) and in further view of Waggoner et al. (U.S. Pat. No. 6,008,373). Applicants respectfully traverse this rejection.

Applicants note that claim 30 depends from claim 1 and thus includes all of the limitations of claim 1. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claim 1 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, (a) there is no disclosure, suggestion, or motivation to make the alleged alteration in the cited publications, the Office Action provides no evidence that supports the conclusion of the rejection that those of skill in the art would be motivated to make the alleged alteration, the alleged (and completely unsupported) motivation recited in the Office Action would not, in fact, motivate the required alteration; (b) the rejection is clearly based on impermissible hindsight as evidenced by the implicit logic of the rejection; and (c) the alleged alteration cannot support the alleged obviousness of the claimed method because the alleged alteration would impermissibly alter a fundamental principle of operation of the method of Lizardi '229.

Waggoner et al. fails to supplement the elements missing from Lizardi '229 and Schweitzer et al. Waggoner et al. was cited for its disclosure of using phycoerythrin as a fluorophore in the detection label on an antibody. Waggoner et al. fails to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, wherein the capture tag is not a nucleic acid, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. Thus, Lizardi '229, Schweitzer et al., and Waggoner et al., either alone or in combination, fail to disclose or suggest each and every element of claim 30. Accordingly, Lizardi '229, Schweitzer et al., and Waggoner et al. do not make obvious claim 30. Applicants respectfully request withdrawal of this rejection.

4. Claims 48-52, and 69 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Cao et al. (U.S. 2002/0120409). Applicants respectfully traverse this rejection.

With regard to claims 48-52, and 69 the Office Action applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a) addressed above. As noted in the Office Action (page 9, lines 13-15) Lizardi '229 and Schweitzer et al. fail to teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA.

Claims 48-52 involve a method of amplifying messenger RNA, involving fragmenting cDNA strands to form fragmented cDNA, adding a capture tag to the fragmented cDNA, mixing the fragmented cDNA with a set of capture probes under conditions that promote hybridization of the fragmented cDNA to the capture probes, mixing one or more rolling circle replication primers with the fragmented cDNA under conditions that promote association of the fragmented cDNA with the rolling circle replication primers, where the association occurs via the capture tag. Thus the claims require adding a capture tag to the fragmented cDNA where a rolling circle replication primer associates with the fragmented cDNA via the capture tag.

Claim 69 involves a method of using messenger RNA, the method comprising replicating one or more amplification target circles to produce one or more tandem sequence DNAs, where each tandem sequence DNA is coupled to a rolling circle replication primer, where the rolling circle replication primer is associated with a fragmented cDNA strand, where the fragmented cDNA strand is hybridized to a capture probe, where the fragmented cDNA comprises a capture tag, where the association of the rolling circle replication primer and the fragmented cDNA strand occurs via the capture tag. Thus, like claims 48-52, claim 69 requires that the fragmented cDNA comprises a capture tag where the rolling circle replication primer associates with the fragmented cDNA strand via the capture tag of the cDNA strand.

For at least the reasons discussed above regarding the rejection of claims 1-15, 18-29, 53-58, 61, 62, 68, 70-73 and 82-87 under 35 U.S.C. § 103(a), Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claims 48-52, and 69. Specifically, (a) there is no disclosure, suggestion, or motivation to make the alleged alteration in the cited publications, the Office Action provides no evidence that supports the conclusion of the rejection that those of skill in the art would be motivated to make the alleged alteration, the alleged (and completely unsupported) motivation recited in the Office Action

would not, in fact, motivate the required alteration; (b) the rejection is clearly based on impermissible hindsight as evidenced by the implicit logic of the rejection; and (c) the alleged alteration cannot support the alleged obviousness of the claimed method because the alleged alteration would impermissibly alter a fundamental principle of operation of the method of Lizardi '229.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin (see Cao et al. claim 1 and paragraphs 0045-0049). The incorporated label then serves as a means of detecting the labeled cDNA (see Cao et al., para. 49). Cao et al. does not disclose or suggest associating rolling circle replication primers with the fragmented cDNA via the labels or any other component. Thus, the label of Cao et al. is not a capture tag as claimed.

Cao et al. fails to supplement the elements missing from Lizardi '229 and Schweitzer et al. Cao et al. was cited for its disclosure of teaching fragmented cDNA in a method to amplify mRNA. Cao et al. fails to disclose or suggest cDNA comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, wherein the capture tag is not a nucleic acid, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. Thus, Lizardi '229, Schweitzer et al., and Cao et al., either alone or in combination, fail to disclose or suggest each and every element of claims 48-52 and 60. Accordingly, Lizardi '229, Schweitzer et al., and Cao et al. do not make obvious claims 48-52 and 60. Applicants respectfully request withdrawal of this rejection.

5. Claims 59 and 60 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) and Schweitzer et al. (PNAS 2000) in view of Shoemaker et al. (U.S. Pat. No. 6,713,257 B2). Applicants respectfully traverse this rejection.

Applicants note that claims 59 and 60 depend from claim 56 and thus include all the limitations of claim 56. Applicants also note that the rejection applies Lizardi '229 and Schweitzer et al. in the same way and for the same disclosures for which Lizardi '229 and Schweitzer et al. were applied in the rejection of claim 1 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Schweitzer et al., either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, (a) there is no disclosure, suggestion, or motivation to make the alleged alteration in the cited

publications, the Office Action provides no evidence that supports the conclusion of the rejection that those of skill in the art would be motivated to make the alleged alteration, the alleged (and completely unsupported) motivation recited in the Office Action would not, in fact, motivate the required alteration; (b) the rejection is clearly based on impermissible hindsight as evidenced by the implicit logic of the rejection; and (c) the alleged alteration cannot support the alleged obviousness of the claimed method because the alleged alteration would impermissibly alter a fundamental principle of operation of the method of Lizardi '229.

Shoemaker et al. fails to supplement the elements missing from Lizardi '229 and Schweitzer et al. Shoemaker et al. was cited for its disclosure of using an amino-allyl dUTP in labeling cDNA. Shoemaker et al. fails to disclose or suggest the use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi '229, Schweitzer et al., and Shoemaker et al., either alone or in combination, fail to disclose or suggest each and every element of claims 59 and 60. Accordingly, Lizardi '229, Schweitzer et al., and Shoemaker et al. do not make obvious claims 59 and 60. Applicants respectfully request withdrawal of this rejection.

A Credit Card Payment authorizing payment in the amount of $475.00, representing $225.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(2) and $250.00 for the fee for a small entity under 37 C.F.R. § 41.20(b)(1); a Request for Two (2) Month Extension of Time; and a Notice of Appeal are also enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

Scott D. Marty, Ph.D.

4.18.07
Date